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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 February 2000 (14.02.00)	
International application No. PCT/US99/13659	**Applicant's or agent's file reference** 15966-514
International filing date (day/month/year) 18 June 1999 (18.06.99)	**Priority date** (day/month/year) 18 June 1998 (18.06.98)
Applicant NANDABALAN, Krishnan et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 January 2000 (18.01.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia RANAIVOJAONA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 99/13659

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/47 C12N9/12 C12N15/62 C12N15/12 C07K16/18
A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 12806 A (UNIV LELAND STANFORD JUNIOR) 2 May 1996 (1996-05-02) page 4, line 6 -page 6, line 23 page 10, line 27 -page 22, line 25 ---	1,40-47
X	WADE HARPER ET AL: "The p21 Cdk-Interacting Protein Cip1 Is a Potent Inhibitor of G1 Cyclin-Dependent Kinases" CELL, vol. 75, no. 75, 19 November 1993 (1993-11-19), pages 805-816 , XP002098279 ISSN: 0092-8674 the whole document --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 1999	10/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Mateo Rosell, A.M.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 18824 A (SLOAN KETTERING INST CANCER ;HUTCHINSON FRED CANCER RES (US)) 13 July 1995 (1995-07-13) page 4, line 28-35 page 7, line 10-32 page 22, line 15-32 page 28, line 19 -page 30, line 30 page 36, line 5-24 page 54, line 25 -page 60, line 30 page 69, line 31 -page 72, line 13 & US 5 688 665 A cited in the application	1,4, 8-12,17, 19,22, 23,60-65
Y	CHIEN C -T ET AL: "THE TWO-HYBRID SYSTEM: A METHOD TO IDENTIFY AND CLONE GENES FOR PROTEINS THAT INTERACT WITH A PROTEIN OF INTEREST" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 88, November 1991 (1991-11), pages 9578-9582, XP002913781 ISSN: 0027-8424 cited in the application the whole document	1,4, 8-12,17, 19,22, 23,60-65
A	POLYAK K ET AL: "CLONING OF P27KIP1, A CYCLIN-DEPENDENT KINASE INHIBITOR AND A POTENTIAL MEDIATOR OF EXTRACELLULAR ANTIMITOGENIC SIGNALS" CELL, vol. 78, 15 July 1994 (1994-07-15), pages 59-66, XP002916569 ISSN: 0092-8674 cited in the application	1,10-12
A	KWON T-K ET AL., : "The cdk2 binding domain of p27kip correlates with the inhibition of the kinase activity of cdk2/cyclin complexes" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 220, 1996, pages 703-709, XP002120285 cited in the application the whole document	1,10-12
A	LUO Y ET AL., : "Rapamycin resistance tied to defective regulation of p27Kip1" MOL CELL BIOL, vol. 16 (12), 1996, page 6744-51 XP002120286 cited in the application the whole document	1,31-39

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 21861 A (MERCK & CO INC) 17 August 1995 (1995-08-17) abstract page 4, line 10-27 page 7, line 9-24 page 16, line 30 -page 18, line 27 page 24, line 22 -page 27, line 30	1,8-12
A	WO 97 15659 A (CORNELL RES FOUNDATION INC) 1 May 1997 (1997-05-01) page 1, line 10 -page 4, line 23	1-9
A	NAKAYAMA K ET AL: "MICE LACKING P27KIP1 DISPLAY INCREASED BODY SIZE, MULTIPLE ORGAN HYPERPLASIA, RETINAL DYSPLASIA, AND PITUITARY TUMORS" CELL, vol. 85, 31 May 1996 (1996-05-31), pages 707-720, XP002056976 ISSN: 0092-8674	48,49
A	DUMONT FJ AND SU Q: "Mechanism of action of the immunosuppressant rapamycin" LIFE SCIENCES, vol. 58 (5), 1996, page 373-395 XP002120287 cited in the application the whole document	1
P,X	DATABASE WPI Section Ch, Week 199932 Derwent Publications Ltd., London, GB; Class B04, AN 1999-375265 XP002120288 & JP 11 142407 A (ARATA N), 28 May 1999 (1999-05-28) abstract	8,9,30

INTERNATIONAL SEARCH REPORT

Ir ıational application No.
PCT/US 99/ 13659

Box I Observations where c rtain claims w re found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Remarks:
Although claims 31-39, 51-53, 59-65 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claim 29 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern ...nal Application No
PCT/US 99/13659

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9612806 A	02-05-1996	US 5723436 A	03-03-1998
		AU 4006695 A	15-05-1996
WO 9518824 A	13-07-1995	US 5688665 A	18-11-1997
		AU 699969 B	17-12-1998
		AU 1525195 A	01-08-1995
		CA 2180570 A	13-07-1995
		EP 0749442 A	27-12-1996
		JP 9509311 T	22-09-1997
		AU 2770695 A	16-02-1996
		WO 9602140 A	01-02-1996
WO 9521861 A	17-08-1995	US 5457182 A	10-10-1995
		CA 2181803 A	17-08-1995
		EP 0749443 A	27-12-1996
		JP 9509160 T	16-09-1997
WO 9715659 A	01-05-1997	AU 7468496 A	15-05-1997
		CA 2229426 A	01-05-1997
		EP 0862621 A	09-09-1998
JP 11142407 A	28-05-1999	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
15966-514		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/13659	18/06/1999	18/06/1998
International Patent Classification (IPC) or national classification and IPC C07K14/47		
Applicant CURAGEN CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/01/2000	18.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lanzrein, M Telephone No. +49 89 2399 7358

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/13659

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-54 as originally filed

Claims, No.:

1-65 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non- stablishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 31-39, 60-65.

because:

☒ the said international application, or the said claims Nos. 31-39, 60-65 relate to the following subj ct matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 2, 5-7, 9-18, 20-30, 40-59
	No:	Claims	3, 4, 8, 19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-30, 40-59
Industrial applicability (IA)	Yes:	Claims	1-30, 40-59
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

s separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 31-39, 60-65 relate to methods for treatment of the human or animal body considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to novelty, inventive step and industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. This application is based on the finding that p27(Kip1) complexes with FKBP-12. Said interaction was found employing a yeast two hybrid assay system. The claims are directed towards the complex and derivatives thereof, antibodies specific for the complex, the DNA sequences of the binding partners, pharmaceutical compositions comprising the complex or antibody, methods for producing the complex, diagnosis methods for diseases related to aberrant levels of the complex, methods for treating such diseases, methods for screening for potential therapeutic compounds related to said complex, and recombinant animals which are altered in either or both genes.

2. Reference is made to the following documents:

   D1: WO 95 18824 A (SLOAN KETTERING INST CANCER ;HUTCHINSON FRED CANCER RES (US)) 13 July 1995 (1995-07-13)
   D2: DUMONT FJ AND SU Q: 'Mechanism of action of the immunosuppressant rapamycin' LIFE SCIENCES, vol. 58 (5), 1996, page 373-395, cited in the application
   D3: CHIEN C -T ET AL: 'THE TWO-HYBRID SYSTEM: A METHOD TO

IDENTIFY AND CLONE GENES FOR PROTEINS THAT INTERACT WITH A PROTEIN OF INTEREST' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 88, November 1991 (1991-11), pages 9578-9582, cited in the application

D4: NAKAYAMA K ET AL: 'MICE LACKING P27KIP1 DISPLAY INCREASED BODY SIZE, MULTIPLE ORGAN HYPERPLASIA, RETINAL DYSPLASIA, AND PITUITARY TUMORS' CELL, vol. 85, 31 May 1996 (1996-05-31), pages 707-720.

3. Claims 3, 4, 8, 19 lack novelty according to Art. 33 (2) PCT.

3.1 Claims 3, and 19 are not new in view of D1. Said claims refer to complexes of derivatives of p27(Kip1) and FKBP-12. In the description it is stated that derivatives include molecules of at least 30% amino acid identity or that the encoding nucleic acids had to be capable of hybridizing under non-stringent conditions. Already this definition is so broad that many known prior art molecules are covered by it. But on top of that, it is even stated that derivatives are not limited to these molecules. Hence, virtually any existing protein molecule is regarded as derivative and falls under the scope of said claims as long as it is able to bind to *wild type* FKBP-12 or *wild type* p27(Kip1), respectively. Cyclin E would therefore be regarded as a derivative falling under said claims, since D1 shows that cyclinE/CdK2 complexes with p27(Kip1). It should be noted that p27(Kip1) was purified in D1 via a cyclinE affinity column, i.e. the column contained a purified cyclinE/p27(Kip1) complex (see e.g. p. 37 l. 16 - p. 38, l. 25). It follows that the cyclinE/CdK2/p27(Kip1) complex of D1 is prejudicial to novelty of claims 3, and 19.

3.2 Claim 4 concerns the complex of claim 3 which is fluorescently labelled. D1 discloses a fluorescently labeled antibody binding to p27(Kip1) (p. 30, l. 10-20). Said antibody would also bind to a complex formed by p27(Kip1) and thereby provide a fluorescently labeled complex. It follows that claim 4 is not new in view of D1.

3.3 Document D1 describes the cloning and expression of p27(Kip1) and includes disclosures of antibodies to said protein (p. 29, l. 12 - p. 30 l. 20). In view of this, claim 8 is not novel because any antibody binding to any of the individual proteins would also bind to the complex.

4. Claims 1-30, 40-59 lack inventive step according to Art. 33 (3) PCT.

4.1 Claims 1-4 concern the complex of p27(Kip1)/FKBP-12 and derivatives thereof. Document D1, which is considered to represent the most relevant state of the art, discloses the cloning, expression and purification of p27(Kip1). It is also known from D1 that p27(Kip1) complexes with the cyclinE/Cdk2 complex. The subject-matter of claims 1-4 differs in that p27(Kip1) is complexed to FKBP-12. The problem to be solved by the present invention may therefore be regarded as the provision of another complex comprising the p27(Kip1) molecule. The solution was to show, in yeast cells, that p27(Kip1) interacts with FKBP-12, and thereby to provide a p27(Kip1)/FKBP-12 complex. However, said solution cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

In D1, it is stated that cells moving towards S-phase have lowered levels of p27(Kip1) protein. The reduction is, however, not associated with reduced mRNA levels of p27(Kip1), suggesting that p27(Kip1) protein is sequestered by binding to a 'silencing' protein (p. 71, l. 28 - p. 72 l. 7). In other words, it was known from D1 that p27(Kip1) was likely to bind to additional proteins, besides its established interaction with cyclinE/Cdk2. To screen for such binding proteins was thus both obvious and desirable, specially because p27(Kip1) is an important regulatory molecule in the cell cycle and therefore a important potential target for cancer therapy. Any protein interacting with p27(Kip1) would therefore be of great interest as possible additional target.

Furthermore, we argue that it was not surprising that FKBP-12 was one of the p27(Kip1)-binding proteins in view of D2. It was known from D2 that there is a link between cyclinE/Cdk2 and immunophilins such as FKBP-12. Data are reviewed in D2 which show that rapamycin, which is an activator of FKBP-12, prevents IL-2 induced p27(Kip1) removal in T-cells (p. 382, l. 9-13). It is even suggested that the effect of rapamycin could be due to interaction of FKBP-12 with mTOR and

p27(Kip1) (see proposed interaction in Fig. 2). Thus, although direct binding of p27(Kip1) and FKBP-12 has not been demonstrated, their connection in terms of cellular signalling was clearly known from D2.
In summary, in view of the plausibility of other proteins interacting with p27(Kip1), it was obvious to the person skilled in the art to screen for such proteins. The two-hybrid screen is a well known and widely used method for this purpose (see D3). In view of the teachings of D2, the skilled person would have anticipated that FKBP-12 may interact with p27(Kip1).

4.2 Claims 5-7, 13 concern a chimeric protein of p27(Kip1) and FKBP-12. This does not establish inventiveness because the construction of fusion proteins is a well known and widely practised standard technique in the art.

4.3 Claims 8, 9 concern an antibody against the p27(Kip1)/FKBP-12-complex. Said antibody is not considered inventive because generation of antibodies is a standard technique known to any persons in the art.

4.4 Claims 10-12, 14-16, 28 relate to nucleotide sequences encoding p27(Kip1) and FKBP-12 , and a method for producing the complex recombinantly. The nucleotide sequences were known. The p27(Kip1)/FKBP-12 complex is not considered inventive (see above) and thus the combination of the corresponding nucleotide sequences and their coexpression does not establish inventive step, because it would be obvious to the skilled person to coexpress both cDNA sequences in a cell in order to obtain the complex.

4.5 Claims 17-27 concern pharmaceutical compositions related to said complex. It was known that both p27(Kip1) (see e.g. D1) and FKBP-12 (see e.g. D2) are related to disease and pharmaceutical compositions involving p27(Kip1) were indeed proposed in D1. It was thus obvious that also the complex of p27(Kip1)/FKBP-12 and related attributes could be useful in pharmaceutical compositions.

4.6 Claims 48-50 concern recombinant non-human animals. The generation of transgenic mice and mice having targeted deletions is standard. Also, double knockouts or transgenics can easily be obtained by crossing in. Furthermore, a

p27(Kip1) knockout mouse already existed and was disclosed in D4. Said claims do therefore not establish inventiveness.

4.7 Claim 29, 30, 40-47, 51-59 refer to embodiments which do not establish inventive step, because they essentially consist of standard applications which are obvious to anyone skilled in the art. Since the main subject matter of the application, i.e. the complex of p27(Kip1) and FKBP-12 was found to be not inventive, said standard applications cannot establish inventiveness.

Re Item VIII

Certain observations on the international application

1. Claims 3, 4, 29, 40-46, 51-59 do not meet the requirements of Art. 6 PCT.

1.1 In claims 3 and 4, the subject matter for which protection is sought is not clear because the term "derivative" is too vague and renders the claim indefinite as already set forth under item 3.1.

1.2 Claims 29, 40-46, 51-59 refer to "functional activity", "biological activity" or simply "activity" of the p27(Kip1)/FKBP-12 complex. These terms are vague and ambiguous. Apart from speculation, the present application does not provide substantial evidence of any activity of said complex. Therefore, the skilled person does not know what kind of activity said claims refer to. Said claims are therefore unclear and not sufficiently disclosed within the meaning of Art. 6 PCT.

2. Claims 29, 44, 46, 59 are ambiguous with respect to wether *in vivo* methods are covered. In case of an European application said claims would not be allowable because methods of treatment of the human or animal body as well as diagnostic methods are not regarded as inventions which are susceptible of industrial application.

However, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.

3. Claims 51-59 do not meet the requirements of Art. 6 PCT because the subject matter is not sufficiently disclosed by the description.

3.1 Claims 51-58 relate to methods for modulation of activities of p27(Kip1), FKBP-12 or both and methods for identifying such modulators. The description does not disclose any experimental data showing that indeed the activity or the levels of p27(Kip1) are affected by "contacting a cell with (..) a FKBP12 protein" or vice versa. Furthermore, there is no clue how to search for molecules that modulate the activity or the level of a complex of p27(Kip1) and FKBP-12. This is only dealt in very general terms, i.e. in terms which are anyway obvious to the skilled person. However, the skilled person would need more detailed and substantive information with regards to candidate compounds and at least one example should be given to illustrate that the principle is working.

3.2 Claim 59 refers to a method for monitoring the efficacy of treatment of a disease characterized by an aberrant level of the p27(Kip1)/FKBP-12 complex. Said method is not enabled because there is no indication that such treatment exists or works at all. It is not known what diseases are related to aberrant levels of the p27(Kip1)/FKBP-12 complex. To claim a method for monitoring a nonexisting treatment of an unknown disease appears to be nonsense.

PATENT COOPERATION TREATY

OCT 23 2000

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ELFIRI, Ivor R.
Mintz, Levin, Cohn, Ferris
Glovsky and Popeo, P.C.
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

Done By
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 18.10.2000
Applicant's or agent's file reference 15966-514-06 \	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/13659	18/06/1999	18/06/1998

Applicant
CURAGEN CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Emslander, S Tel.+49 89 2399-8718

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
15966-514		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/13659	18/06/1999	18/06/1998
International Patent Classification (IPC) or national classification and IPC C07K14/47		
Applicant CURAGEN CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/01/2000	18.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lanzrein, M Telephone No. +49 89 2399 7358

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/13659

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-54 as originally filed

Claims, No.:

1-65 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 31-39, 60-65.

because:

☒ the said international application, or the said claims Nos. 31-39, 60-65 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Rea oned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 2, 5-7, 9-18, 20-30, 40-59
	No:	Claims	3, 4, 8, 19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-30, 40-59
Industrial applicability (IA)	Yes:	Claims	1-30, 40-59
	No:	Claims	

2. Citations and explanations

s e separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

s separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 31-39, 60-65 relate to methods for treatment of the human or animal body considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to novelty, inventive step and industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. This application is based on the finding that p27(Kip1) complexes with FKBP-12. Said interaction was found employing a yeast two hybrid assay system. The claims are directed towards the complex and derivatives thereof, antibodies specific for the complex, the DNA sequences of the binding partners, pharmaceutical compositions comprising the complex or antibody, methods for producing the complex, diagnosis methods for diseases related to aberrant levels of the complex, methods for treating such diseases, methods for screening for potential therapeutic compounds related to said complex, and recombinant animals which are altered in either or both genes.

2. Reference is made to the following documents:

   D1: WO 95 18824 A (SLOAN KETTERING INST CANCER ;HUTCHINSON FRED CANCER RES (US)) 13 July 1995 (1995-07-13)
   D2: DUMONT FJ AND SU Q: 'Mechanism of action of the immunosuppressant rapamycin' LIFE SCIENCES, vol. 58 (5), 1996, page 373-395, cited in the application
   D3: CHIEN C -T ET AL: 'THE TWO-HYBRID SYSTEM: A METHOD TO

IDENTIFY AND CLONE GENES FOR PROTEINS THAT INTERACT WITH A PROTEIN OF INTEREST' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 88, November 1991 (1991-11), pages 9578-9582, cited in the application

D4: NAKAYAMA K ET AL: 'MICE LACKING P27KIP1 DISPLAY INCREASED BODY SIZE, MULTIPLE ORGAN HYPERPLASIA, RETINAL DYSPLASIA, AND PITUITARY TUMORS' CELL, vol. 85, 31 May 1996 (1996-05-31), pages 707-720.

3. Claims 3, 4, 8, 19 lack novelty according to Art. 33 (2) PCT.

3.1 Claims 3, and 19 are not new in view of D1. Said claims refer to complexes of derivatives of p27(Kip1) and FKBP-12. In the description it is stated that derivatives include molecules of at least 30% amino acid identity or that the encoding nucleic acids had to be capable of hybridizing under non-stringent conditions. Already this definition is so broad that many known prior art molecules are covered by it. But on top of that, it is even stated that derivatives are not limited to these molecules. Hence, virtually any existing protein molecule is regarded as derivative and falls under the scope of said claims as long as it is able to bind to *wild type* FKBP-12 or *wild type* p27(Kip1), respectively. Cyclin E would therefore be regarded as a derivative falling under said claims, since D1 shows that cyclinE/CdK2 complexes with p27(Kip1). It should be noted that p27(Kip1) was purified in D1 via a cyclinE affinity column, i.e. the column contained a purified cyclinE/p27(Kip1) complex (see e.g. p. 37 l. 16 - p. 38, l. 25). It follows that the cyclinE/CdK2/p27(Kip1) complex of D1 is prejudicial to novelty of claims 3, and 19.

3.2 Claim 4 concerns the complex of claim 3 which is fluorescently labelled. D1 discloses a fluorescently labeled antibody binding to p27(Kip1) (p. 30, l. 10-20). Said antibody would also bind to a complex formed by p27(Kip1) and thereby provide a fluorescently labeled complex. It follows that claim 4 is not new in view of D1.

3.3 Document D1 describes the cloning and expression of p27(Kip1) and includes disclosures of antibodies to said protein (p. 29, l. 12 - p. 30 l. 20). In view of this, claim 8 is not novel because any antibody binding to any of the individual proteins would also bind to the complex.

4. Claims 1-30, 40-59 lack inventive step according to Art. 33 (3) PCT.

4.1 Claims 1-4 concern the complex of p27(Kip1)/FKBP-12 and derivatives thereof. Document D1, which is considered to represent the most relevant state of the art, discloses the cloning, expression and purification of p27(Kip1). It is also known from D1 that p27(Kip1) complexes with the cyclinE/Cdk2 complex. The subject-matter of claims 1-4 differs in that p27(Kip1) is complexed to FKBP-12. The problem to be solved by the present invention may therefore be regarded as the provision of another complex comprising the p27(Kip1) molecule. The solution was to show, in yeast cells, that p27(Kip1) interacts with FKBP-12, and thereby to provide a p27(Kip1)/FKBP-12 complex. However, said solution cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

In D1, it is stated that cells moving towards S-phase have lowered levels of p27(Kip1) protein. The reduction is, however, not associated with reduced mRNA levels of p27(Kip1), suggesting that p27(Kip1) protein is sequestered by binding to a 'silencing' protein (p. 71, l. 28 - p. 72 l. 7). In other words, it was known from D1 that p27(Kip1) was likely to bind to additional proteins, besides its established interaction with cyclinE/Cdk2. To screen for such binding proteins was thus both obvious and desirable, specially because p27(Kip1) is an important regulatory molecule in the cell cycle and therefore a important potential target for cancer therapy. Any protein interacting with p27(Kip1) would therefore be of great interest as possible additional target.

Furthermore, we argue that it was not surprising that FKBP-12 was one of the p27(Kip1)-binding proteins in view of D2. It was known from D2 that there is a link between cyclinE/Cdk2 and immunophilins such as FKBP-12. Data are reviewed in D2 which show that rapamycin, which is an activator of FKBP-12, prevents IL-2 induced p27(Kip1) removal in T-cells (p. 382, l. 9-13). It is even suggested that the effect of rapamycin could be due to interaction of FKBP-12 with mTOR and

p27(Kip1) (see proposed interaction in Fig. 2). Thus, although direct binding of p27(Kip1) and FKBP-12 has not been demonstrated, their connection in terms of cellular signalling was clearly known from D2.
In summary, in view of the plausibility of other proteins interacting with p27(Kip1), it was obvious to the person skilled in the art to screen for such proteins. The two-hybrid screen is a well known and widely used method for this purpose (see D3). In view of the teachings of D2, the skilled person would have anticipated that FKBP-12 may interact with p27(Kip1).

4.2 Claims 5-7, 13 concern a chimeric protein of p27(Kip1) and FKBP-12. This does not establish inventiveness because the construction of fusion proteins is a well known and widely practised standard technique in the art.

4.3 Claims 8, 9 concern an antibody against the p27(Kip1)/FKBP-12-complex. Said antibody is not considered inventive because generation of antibodies is a standard technique known to any persons in the art.

4.4 Claims 10-12, 14-16, 28 relate to nucleotide sequences encoding p27(Kip1) and FKBP-12 , and a method for producing the complex recombinantly. The nucleotide sequences were known. The p27(Kip1)/FKBP-12 complex is not considered inventive (see above) and thus the combination of the corresponding nucleotide sequences and their coexpression does not establish inventive step, because it would be obvious to the skilled person to coexpress both cDNA sequences in a cell in order to obtain the complex.

4.5 Claims 17-27 concern pharmaceutical compositions related to said complex. It was known that both p27(Kip1) (see e.g. D1) and FKBP-12 (see e.g. D2) are related to disease and pharmaceutical compositions involving p27(Kip1) were indeed proposed in D1. It was thus obvious that also the complex of p27(Kip1)/FKBP-12 and related attributes could be useful in pharmaceutical compositions.

4.6 Claims 48-50 concern recombinant non-human animals. The generation of transgenic mice and mice having targeted deletions is standard. Also, double knockouts or transgenics can easily be obtained by crossing in. Furthermore, a

p27(Kip1) knockout mouse already existed and was disclosed in D4. Said claims do therefore not establish inventiveness.

4.7 Claim 29, 30, 40-47, 51-59 refer to embodiments which do not establish inventive step, because they essentially consist of standard applications which are obvious to anyone skilled in the art. Since the main subject matter of the application, i.e. the complex of p27(Kip1) and FKBP-12 was found to be not inventive, said standard applications cannot establish inventiveness.

Re Item VIII

Certain observations on the international application

1. Claims 3, 4, 29, 40-46, 51-59 do not meet the requirements of Art. 6 PCT.

1.1 In claims 3 and 4, the subject matter for which protection is sought is not clear because the term "derivative" is too vague and renders the claim indefinite as already set forth under item 3.1.

1.2 Claims 29, 40-46, 51-59 refer to "functional activity", "biological activity" or simply "activity" of the p27(Kip1)/FKBP-12 complex. These terms are vague and ambiguous. Apart from speculation, the present application does not provide substantial evidence of any activity of said complex. Therefore, the skilled person does not know what kind of activity said claims refer to. Said claims are therefore unclear and not sufficiently disclosed within the meaning of Art. 6 PCT.

2. Claims 29, 44, 46, 59 are ambiguous with respect to wether *in vivo* methods are covered. In case of an European application said claims would not be allowable because methods of treatment of the human or animal body as well as diagnostic methods are not regarded as inventions which are susceptible of industrial application.

However, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.

3. Claims 51-59 do not meet the requirements of Art. 6 PCT because the subject matter is not sufficiently disclosed by the description.

3.1 Claims 51-58 relate to methods for modulation of activities of p27(Kip1), FKBP-12 or both and methods for identifying such modulators. The description does not disclose any experimental data showing that indeed the activity or the levels of p27(Kip1) are affected by "contacting a cell with (..) a FKBP12 protein" or vice versa. Furthermore, there is no clue how to search for molecules that modulate the activity or the level of a complex of p27(Kip1) and FKBP-12. This is only dealt in very general terms, i.e. in terms which are anyway obvious to the skilled person. However, the skilled person would need more detailed and substantive information with regards to candidate compounds and at least one example should be given to illustrate that the principle is working.

3.2 Claim 59 refers to a method for monitoring the efficacy of treatment of a disease characterized by an aberrant level of the p27(Kip1)/FKBP-12 complex. Said method is not enabled because there is no indication that such treatment exists or works at all. It is not known what diseases are related to aberrant levels of the p27(Kip1)/FKBP-12 complex. To claim a method for monitoring a nonexisting treatment of an unknown disease appears to be nonsense.

PATENT COOPERATION TREA

RECEIVED

From the INTERNATIONAL SEARCHING AUTHORITY

PCT NOV 15 1999

To:
Mintz, Levin, Cohn, Ferris
Glovsky and Popeo, P.C.
Attn. ELFIRI, I.
One Financial Center
Boston, MA 02111
UNITED STATES OF AMERICA

☐ File Folder
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MINTZ LEVIN BOSTON
BOSTON DOCKET DEPT.

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 10/11/1999
Applicant's or agent's file reference 15966-514	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 99/13659	International filing date *(day/month/year)* 18/06/1999
Applicant CURAGEN CORPORATION et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from th priority dat or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Chantal Meyer

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
15966-514		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 13659	18/06/1999	18/06/1998
Applicant		
CURAGEN CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of th **drawings** to be published with th abstract is Figure No. 3

[X] as suggested by the applicant.

[ ] None of th figures.

[ ] because th applicant failed to suggest a figure.

[ ] because this figure better characterizes th invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 13659

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Remarks:
Although claims 31-39, 51-53, 59-65 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claim 29 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/13659

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/47 C12N9/12 C12N15/62 C12N15/12 C07K16/18
A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 12806 A (UNIV LELAND STANFORD JUNIOR) 2 May 1996 (1996-05-02) page 4, line 6 -page 6, line 23 page 10, line 27 -page 22, line 25	1,40-47
X	WADE HARPER ET AL: "The p21 Cdk-Interacting Protein Cip1 Is a Potent Inhibitor of G1 Cyclin-Dependent Kinases" CELL, vol. 75, no. 75, 19 November 1993 (1993-11-19), pages 805-816 , XP002098279 ISSN: 0092-8674 the whole document	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 1999	10/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Mateo Rosell, A.M.

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 18824 A (SLOAN KETTERING INST CANCER ;HUTCHINSON FRED CANCER RES (US)) 13 July 1995 (1995-07-13) page 4, line 28-35 page 7, line 10-32 page 22, line 15-32 page 28, line 19 -page 30, line 30 page 36, line 5-24 page 54, line 25 -page 60, line 30 page 69, line 31 -page 72, line 13 & US 5 688 665 A cited in the application	1,4, 8-12,17, 19,22, 23,60-65
Y	CHIEN C -T ET AL: "THE TWO-HYBRID SYSTEM: A METHOD TO IDENTIFY AND CLONE GENES FOR PROTEINS THAT INTERACT WITH A PROTEIN OF INTEREST" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 88, November 1991 (1991-11), pages 9578-9582, XP002913781 ISSN: 0027-8424 cited in the application the whole document	1,4, 8-12,17, 19,22, 23,60-65
A	POLYAK K ET AL: "CLONING OF P27KIP1, A CYCLIN-DEPENDENT KINASE INHIBITOR AND A POTENTIAL MEDIATOR OF EXTRACELLULAR ANTIMITOGENIC SIGNALS" CELL, vol. 78, 15 July 1994 (1994-07-15), pages 59-66, XP002916569 ISSN: 0092-8674 cited in the application	1,10-12
A	KWON T-K ET AL., : "The cdk2 binding domain of p27kip correlates with the inhibition of the kinase activity of cdk2/cyclin complexes" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 220, 1996, pages 703-709, XP002120285 cited in the application the whole document	1,10-12
A	LUO Y ET AL., : "Rapamycin resistance tied to defective regulation of p27Kip1" MOL CELL BIOL, vol. 16 (12), 1996, page 6744-51 XP002120286 cited in the application the whole document	1,31-39

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 21861 A (MERCK & CO INC) 17 August 1995 (1995-08-17) abstract page 4, line 10-27 page 7, line 9-24 page 16, line 30 -page 18, line 27 page 24, line 22 -page 27, line 30	1,8-12
A	WO 97 15659 A (CORNELL RES FOUNDATION INC) 1 May 1997 (1997-05-01) page 1, line 10 -page 4, line 23	1-9
A	NAKAYAMA K ET AL: "MICE LACKING P27KIP1 DISPLAY INCREASED BODY SIZE, MULTIPLE ORGAN HYPERPLASIA, RETINAL DYSPLASIA, AND PITUITARY TUMORS" CELL, vol. 85, 31 May 1996 (1996-05-31), pages 707-720, XP002056976 ISSN: 0092-8674	48,49
A	DUMONT FJ AND SU Q: "Mechanism of action of the immunosuppressant rapamycin" LIFE SCIENCES, vol. 58 (5), 1996, page 373-395 XP002120287 cited in the application the whole document	1
P,X	DATABASE WPI Section Ch, Week 199932 Derwent Publications Ltd., London, GB; Class B04, AN 1999-375265 XP002120288 & JP 11 142407 A (ARATA N), 28 May 1999 (1999-05-28) abstract	8,9,30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/13659

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9612806	A	02-05-1996	US	5723436 A	03-03-1998
			AU	4006695 A	15-05-1996
WO 9518824	A	13-07-1995	US	5688665 A	18-11-1997
			AU	699969 B	17-12-1998
			AU	1525195 A	01-08-1995
			CA	2180570 A	13-07-1995
			EP	0749442 A	27-12-1996
			JP	9509311 T	22-09-1997
			AU	2770695 A	16-02-1996
			WO	9602140 A	01-02-1996
WO 9521861	A	17-08-1995	US	5457182 A	10-10-1995
			CA	2181803 A	17-08-1995
			EP	0749443 A	27-12-1996
			JP	9509160 T	16-09-1997
WO 9715659	A	01-05-1997	AU	7468496 A	15-05-1997
			CA	2229426 A	01-05-1997
			EP	0862621 A	09-09-1998
JP 11142407	A	28-05-1999	NONE		

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
15966-514		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 13659	18/06/1999	18/06/1998
Applicant		
CURAGEN CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 3

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 13659

Box I Observations where certain claims wer found unsearchable (Continuation of item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Remarks:
Although claims 31-39, 51-53, 59-65 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claim 29 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/13659

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/47 C12N9/12 C12N15/62 C12N15/12 C07K16/18
A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 12806 A (UNIV LELAND STANFORD JUNIOR) 2 May 1996 (1996-05-02) page 4, line 6 -page 6, line 23 page 10, line 27 -page 22, line 25 ---	1,40-47
X	WADE HARPER ET AL: "The p21 Cdk-Interacting Protein Cip1 Is a Potent Inhibitor of G1 Cyclin-Dependent Kinases" CELL, vol. 75, no. 75, 19 November 1993 (1993-11-19), pages 805-816 , XP002098279 ISSN: 0092-8674 the whole document --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 1999	10/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 18824 A (SLOAN KETTERING INST CANCER ;HUTCHINSON FRED CANCER RES (US)) 13 July 1995 (1995-07-13) page 4, line 28-35 page 7, line 10-32 page 22, line 15-32 page 28, line 19 -page 30, line 30 page 36, line 5-24 page 54, line 25 -page 60, line 30 page 69, line 31 -page 72, line 13 & US 5 688 665 A cited in the application	1,4, 8-12,17, 19,22, 23,60-65
Y	CHIEN C -T ET AL: "THE TWO-HYBRID SYSTEM: A METHOD TO IDENTIFY AND CLONE GENES FOR PROTEINS THAT INTERACT WITH A PROTEIN OF INTEREST" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 88, November 1991 (1991-11), pages 9578-9582, XP002913781 ISSN: 0027-8424 cited in the application the whole document	1,4, 8-12,17, 19,22, 23,60-65
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A	KWON T-K ET AL., : "The cdk2 binding domain of p27kip correlates with the inhibition of the kinase activity of cdk2/cyclin complexes" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 220, 1996, pages 703-709, XP002120285 cited in the application the whole document	1,10-12
A	LUO Y ET AL., : "Rapamycin resistance tied to defective regulation of p27Kip1" MOL CELL BIOL, vol. 16 (12), 1996, page 6744-51 XP002120286 cited in the application the whole document	1,31-39

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 21861 A (MERCK & CO INC) 17 August 1995 (1995-08-17) abstract page 4, line 10-27 page 7, line 9-24 page 16, line 30 -page 18, line 27 page 24, line 22 -page 27, line 30	1,8-12
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A	NAKAYAMA K ET AL: "MICE LACKING P27KIP1 DISPLAY INCREASED BODY SIZE, MULTIPLE ORGAN HYPERPLASIA, RETINAL DYSPLASIA, AND PITUITARY TUMORS" CELL, vol. 85, 31 May 1996 (1996-05-31), pages 707-720, XP002056976 ISSN: 0092-8674	48,49
A	DUMONT FJ AND SU Q: "Mechanism of action of the immunosuppressant rapamycin" LIFE SCIENCES, vol. 58 (5), 1996, page 373-395 XP002120287 cited in the application the whole document	1
P,X	DATABASE WPI Section Ch, Week 199932 Derwent Publications Ltd., London, GB; Class B04, AN 1999-375265 XP002120288 & JP 11 142407 A (ARATA N), 28 May 1999 (1999-05-28) abstract	8,9,30

INTERNATIONAL SEARCH REPORT

rmation on patent family members

International Application No
CT/US 99/13659

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9612806 A	02-05-1996	US 5723436 A	03-03-1998
		AU 4006695 A	15-05-1996
WO 9518824 A	13-07-1995	US 5688665 A	18-11-1997
		AU 699969 B	17-12-1998
		AU 1525195 A	01-08-1995
		CA 2180570 A	13-07-1995
		EP 0749442 A	27-12-1996
		JP 9509311 T	22-09-1997
		AU 2770695 A	16-02-1996
		WO 9602140 A	01-02-1996
WO 9521861 A	17-08-1995	US 5457182 A	10-10-1995
		CA 2181803 A	17-08-1995
		EP 0749443 A	27-12-1996
		JP 9509160 T	16-09-1997
WO 9715659 A	01-05-1997	AU 7468496 A	15-05-1997
		CA 2229426 A	01-05-1997
		EP 0862621 A	09-09-1998
JP 11142407 A	28-05-1999	NONE	